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In-Stent Restenosis and Remote Coronary Lesion Progression Are Coupled in Cardiac Transplant Vasculopathy But Not in Native Coronary Artery Disease

Michael Jonas, MD,*†‡ James C. Fang, MD,* John C. Wang, MD,* Satyendra Giri, MD,* Dan Elian, MD,† Yedael Har-Zahav, MD,† Hung Ly, MD,* Philip A. Seifert, MS,‡ Jeffrey J. Popma, MD,* Campbell Rogers, MD*‡

Boston and Cambridge, Massachusetts; and Tel Hashomer, Israel

OBJECTIVES The purpose of this study was to describe the clinical, angiographic, and histological features of concomitant in-stent restenosis (ISR) and cardiac allograft vasculopathy (CAV) progression.

BACKGROUND Cardiac allograft vasculopathy is a major challenge to long-term success of heart transplantation. Coronary stenting for CAV is hampered by ISR.

METHODS Quantitative coronary angiography compared late lumen loss (LL) at stented and reference, non-stented segments during 1-year follow-up in post-heart transplant and control atherosclerosis patients. Stented and non-stented arteries with CAV were also obtained post-mortem for immunohistochemical analysis.

RESULTS In 37 stented lesions (25 patients), 1-year binary restenosis occurred in 37.8%. Patients with ISR had higher long-term cardiac death/myocardial infarction rates than patients without ISR (53.8% vs. 9.1%, $p = 0.03$). In the same 25 patients, 34 CAV lesions with non-significant obstructions were identified as reference controls. After 1 year, patients who developed ISR also had more control lesion LL (0.78 ± 0.38 mm vs. 0.39 ± 0.27 mm, $p < 0.006$) compared to patients without ISR. In the post-transplant patients, in-stent LL was closely coupled to control segment LL ($R^2 = 0.63$, $p < 0.05$). Conversely, in native atherosclerosis patients, ISR and remote disease progression were not correlated. Histological staining of stented and control arteries from CAV patients revealed similar pathologies common to ISR and non-intervened CAV segments.

CONCLUSIONS Progression of CAV at non-intervened segments and ISR correlate strongly and share common histopathology. Optimized treatment for patients with aggressive CAV needs to address the widespread nature of this disease, even when it presents as an initially focal lesion. (J Am Coll Cardiol 2006;48:453–61) © 2006 by the American College of Cardiology Foundation

Cardiac allograft vasculopathy (CAV) continues to be the major therapeutic challenge and poses significant limitations for long-term survival after heart transplantation (1). Although percutaneous coronary intervention (PCI) with stenting appears to be an attractive treatment for select patients with focal CAV, it does not halt disease progression elsewhere in the coronary vasculature, and its effect on long-term allograft survival remains questionable (2,3). Multiple non-randomized, single-center studies have evaluated the role of PCI (angioplasty or stenting) for CAV and have generally demonstrated excellent acute results but high restenosis rates (2–7).

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The pathogenesis of CAV remains poorly defined and is thought to be a consequence of both immune and non-immune processes (1,8,9). Cardiac allograft vasculopathy is most commonly associated with diffuse concentric intimal hyperplasia, involving both epicardial and intramyocardial coronary arteries, although focal coronary lesions may develop. Histologically, CAV is characterized by inflammatory cell infiltration and smooth muscle cell hyperplasia with a paucity of frank atheroma, histological features reminiscent of the proliferative inflammatory lesions of in-stent restenosis (ISR). Success with sirolimus-coated stents for preventing ISR and oral sirolimus for preventing CAV may also suggest a pathophysiologic link. Although the pathogeneses of both allograft vasculopathy and ISR share such common features, they have not been examined concomitantly and serially over time in human subjects. Therefore, the purpose of the present study was to describe the clinical, angiographic, and histological features of CAV and ISR occurring simultaneously in cardiac transplant recipients. We hypothesized that the response to coronary stenting after cardiac transplantation would parallel the course of CAV in sites distant to stented segments, in a manner not seen in native atherosclerosis (non-CAV) patients undergoing PCI.

METHODS

Patient population. We reviewed medical records of all 30 heart transplant patients who had stent PCI between 1996

From the *Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; †Heart Institute, Sheba Medical Center, Tel Hashomer, Israel; and the ‡Harvard–MIT Division of Health Sciences and Technology, Cambridge, Massachusetts.

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Abbreviations and Acronyms

CAV = cardiac allograft vasculopathy
DES = drug-eluting stent
DS = diameter stenosis
ISR = in-stent restenosis
IVUS = intravascular ultrasound
LL = late lumen loss
MI = myocardial infarction
MLD = minimal lumen diameter
PCI = percutaneous coronary intervention
QCA = quantitative coronary angiography

and 2002 at Brigham and Women's Hospital, Boston, Massachusetts (19 patients) and Sheba Medical Center, Tel-Hashomer, Israel (11 patients). At both institutions, annual surveillance coronary angiography is performed as routine clinical practice in all heart transplant recipients. Of the 30 PCI patients, 25 also had 1-year follow-up coronary angiography. The remaining 5 patients died before the first yearly follow-up angiography and were not included in our analysis. Five of the 25 transplant patients underwent multivessel PCI (a staged procedure in 3) wherein 2 to 4 lesions were stented. Thus, 37 stented lesions in 25 patients with angiographic follow-up form the basis for this analysis. Triple-drug immunosuppression consisting of cyclosporine, azathioprine or mycophenolate mofetil, and prednisone was used as the standard regimen at both centers. A control group of native coronary atherosclerosis patients undergoing PCI with 9-month angiographic follow-up was collected from SIRIUS (Sirolimus-Eluting Stent in de Novo Coronary Lesions Study) (10), a randomized trial comparing sirolimus-eluting stents with bare-metal stents in the U.S. Index and follow-up angiographic films from a cohort of 36 bare-metal–stented patients, matched to the post-transplant group according to stented segment locations, were studied.

Angiographic analysis. All angiograms from post-transplant and SIRIUS control patients were analyzed at the Angiographic Core Laboratory at Brigham and Women's Hospital by 2 experienced angiographers blinded to follow-up outcomes. Qualitative analysis of baseline native vessel morphology was performed using standard criteria and the modified American College of Cardiology/American Heart Association lesion complexity score (11,12).

Angiographic analysis included correlation of ISR and remote CAV or native atherosclerosis progression. For each patient, the flow-limiting stenosis treated with stenting was matched with a non–flow-limiting lesion (<50% diameter stenosis [DS]) in a non-intervened allograft artery, with similar reference diameter chosen to represent a "control" lesion. The control site was chosen on the baseline angiogram, before viewing or analysis of any follow-up angiograms (13). One patient with 4 stented lesions had just 2 matched reference segments due to angiographic core lab technical issues regarding matching vessel size, location, and lesion length. Similarly, another patient undergoing stenting of 3 lesions had just 2 matched reference segments.

Both stented and control segments were then analyzed on baseline and follow-up angiograms, and late lumen loss (LL) for each lesion was determined. The Cardiovascular Measurement System (MEDIS, Leiden, the Netherlands) was used for off-line quantitative cineangiographic analysis. The filled diagnostic or guiding catheter was used as the calibration standard.

Reference vessel diameter segments were calculated by selecting a smooth arterial segment 10 mm proximal to the lesion and 10 mm distal to the lesion from 2 orthogonal views using quantitative coronary angiography (QCA). The mean reference segment diameter, mean minimal lumen diameter (MLD), and mean percent DS before, after, and late following the index procedure were calculated from an average of the 2 angiographic projections. In addition, the single angiographic projection demonstrating the stenosis in its "worst view" was recorded. In-lesion MLD measurement was defined as the mean MLD derived from 2 orthogonal views (by the QCA) in the treated segment and also included an additional 5 mm of proximal and distal edge to evaluate any edge effect. Lesion success is defined as the attainment of <50% residual stenosis (by QCA). Restenosis was defined as >50% in-stent diameter stenosis at the follow-up angiogram. Late loss was defined as the difference between the in-stent MLD at follow-up angiography and the in-stent MLD immediately after the procedure.

Two post-transplant patients (2 stented segments) with available clinical and angiographic follow-up had technically incomplete imaging and were excluded from late loss correlation analysis. In addition, 2 stented and 1 reference segments from the transplant group and 1 stented segment from the native atherosclerosis group were totally occluded at follow-up angiography and hence excluded from late loss calculations.

Histopathology analysis. Stented and non-stented human coronary arteries were obtained at post-mortem examination from 2 patients. Arteries were fixed in 10% neutral buffered formalin, radiographed, and processed for light microscopy by embedding in a methacrylate formulation as previously described (14). Multiple 5-μm-thick sections were cut with a tungsten carbide knife (Delaware Diamond Knives, Wilmington, Delaware) on an automated microtome (Leica, Lasertechnik GmH, Heidelberg, Germany) from the proximal and distal ends and the midpoint of each vessel. Histologic sections were stained with hematoxylin-eosin, Verhoeff elastin, Carstair's fibrin, and Sirius red stain. Vascular inflammatory response was assessed by CD-68 immunostaining.

Statistical analysis. Normally distributed data are reported as mean ± standard deviation. Differences among categorical variables were assessed using the chi-square or Fisher exact test. The two-sided Fisher exact test was used to assess categorical variables when any of the observed responses numbered <5. An unpaired Student t test was used to define differences among continuous variables in sub-groups. The non-

parametric Spearman rank-correlation coefficient was used to estimate the correlation between the in-stent late loss and reference segment late loss.

RESULTS

Clinical and angiographic variables. The 1-year binary angiographic restenosis rate in the heart transplant stented patients was 37.8% (14 of 37 lesions). There were no significant differences in clinical characteristics among patients who did or did not develop restenosis (Table 1). Similarly, the medical regimen, cytomegalovirus status, and number of rejection episodes requiring increased immunosuppression in the year after stenting were comparable between the 2 groups. Stented lesions that developed restenosis tended to have more severe pre-procedure DS and smaller MLD. As expected, LL was significantly greater in restenotic lesions (1.73 ± 0.58 mm vs. 0.46 ± 0.31 mm, $p < 0.001$) (Table 1).

Concurrent ISR and reference vessel disease progression. ALLOGRAFT VASCULOPATHY. In order to evaluate transplant vascular disease progression, a total of 34 lesions in non-intervened allograft coronary arteries with non-

Table 1. Demographic, Clinical, Procedural, and Angiographic Variables of Patients With and Without In-Stent Restenosis

	Restenosis, n = 14 (14 Lesions)	No Restenosis, n = 11 (23 Lesions)	p Value
Clinical characteristics			
Male (%)	85.7	90.9	1.0
Age (yrs)			
At transplant	46.9 ± 8.0	53.0 ± 8.7	0.09
At stenting	53.4 ± 8.7	58.6 ± 9.0	0.15
Stenting (yrs post-transplant)	6.4 ± 2.8	5.6 ± 2.8	0.49
Underlying ischemic cardiomyopathy (%)	76.9	45.5	0.21
Hypertension (%)	38.5	18.2	0.38
Diabetes (treated) (%)	30.8	27.3	1.0
Creatinine at stenting	2.2 ± 2.2	1.6 ± 0.3	0.35
Left ventricular ejection fraction at stenting (%)	47.7 ± 14.2	51.8 ± 9.7	0.40
Patients with rejections ≥ grade 3A (%)	69.2	54.5	0.65
Episodes per patient with rejection	1.4 ± 1.3	1.1 ± 1.7	0.65
Positive CMV serology (%)			
Donor	33.3	18.2	0.64
Recipient	69.2	72.4	1.0
CMV disease	0	0	1.0
Medication (%)			
Azathioprine	92.3	100	1.0
Mycophenolate mofetil	23.1	27.3	1.0
Cyclosporine	100	100	1.0
Prednisone	84.6	90.9	1.0
Gancyclovir	0	18.2	1.0
Statin	91.7	81.8	0.59
Procedural characteristics			
Stented artery (%)			
LAD	55.6	27.3	
CX	16.7	36.4	
RCA	27.8	36.4	0.29
Lesion length (mm)	23.96 ± 13.09	21.02 ± 7.46	0.48
Pre-procedure			
RVD (mm)	2.43 ± 0.43	2.64 ± 0.33	0.13
DS (%)	87 ± 12	80 ± 10	0.08
MLD (mm)	0.30 ± 0.3	0.52 ± 0.26	0.04
Post-procedure			
RVD (mm)	2.63 ± 0.33	2.73 ± 0.34	0.41
DS (%)	14 ± 9	14 ± 9	0.98
MLD (mm)	2.21 ± 0.37	2.29 ± 0.52	0.59
Acute gain (mm)	1.73 ± 0.69	1.77 ± 0.52	0.46
Follow-up			
RVD (mm)	2.45 ± 0.38	2.61 ± 0.29	0.22
DS (%)	79 ± 17	26 ± 10	<0.001
MLD (mm)	0.48 ± 0.39	1.93 ± 0.34	<0.001
Late loss (mm)	1.73 ± 0.58	0.46 ± 0.31	<0.001
Late loss index	0.94 ± 0.30	0.24 ± 0.16	<0.01

CMV = cytomegalovirus; CX = circumflex artery; DS = diameter stenosis; LAD = left anterior descending coronary artery; MLD = minimal lumen diameter; RCA = right coronary artery; RVD = reference vessel diameter.

Table 2. Characteristics of Reference Lesions, According to Whether Restenosis Developed in Stented Site

	Reference of Restenosis Lesions, n = 13	Reference of Non-Restenosis Lesions, n = 21	p Value
Pre-procedure			
RVD (mm)	2.56 ± 0.34	2.64 ± 0.37	0.86
DS (%)	27.70 ± 13.72	22.32 ± 11.18	0.25
MLD (mm)	1.85 ± 0.44	1.97 ± 0.40	0.44
Follow-up			
RVD (mm)	2.41 ± 0.45	2.51 ± 0.38	0.5
DS (%)	52.08 ± 29.47	34.81 ± 20.42	0.07
MLD (mm)	1.17 ± 0.80	1.64 ± 0.55	0.07
Late loss (mm)	0.78 ± 0.38	0.39 ± 0.27	0.006

Abbreviations as in Table 1.

significant (<50% DS) lumen narrowing were used as non-PCI control vessels. Characteristics of these non-PCI lesions are shown in Table 2, according to whether restenosis developed in the same patient's stented site. At baseline, the non-PCI lesions were similar between the 2 groups. At follow-up angiography, the non-PCI lesions from transplant patients who developed ISR had more LL (0.78 ± 0.38 mm vs. 0.39 ± 0.27 mm, $p < 0.006$) and smaller MLD compared to the non-PCI lesions of patients without ISR (Table 2).

The cumulative frequency distribution curves of MLD measured at baseline and follow-up, for both PCI segments and control non-PCI segments, are shown in Figure 1. Although late loss was greater in the stented segments, both the stented and control segments demonstrate a loss of MLD over time.

For each individual heart transplant patient, in-stent late loss directly correlated with late loss of the matched control segment, in both the Sheba Medical Center and the Brigham and Women's patient populations ($R^2 = 0.63$, $p < 0.05$) (Fig. 2A).

NATIVE CORONARY ATHEROSCLEROSIS. In the cohort of native atherosclerosis (non-CAV) patients undergoing PCI, the angiographic restenosis rate was 27.8% (10 of 36 lesions). As for the post-transplant patients, concurrent ISR and atherosclerotic lesion progression in a non-intervened segment were analyzed at baseline and at follow-up. Stented lesions that developed restenosis tended to be longer and have slightly more post-procedure DS. As expected, in-stent LL was significantly greater in restenotic lesions (1.72 ± 0.32 mm vs. 0.57 ± 0.53 mm, $p < 0.001$). At baseline, the control, non-PCI

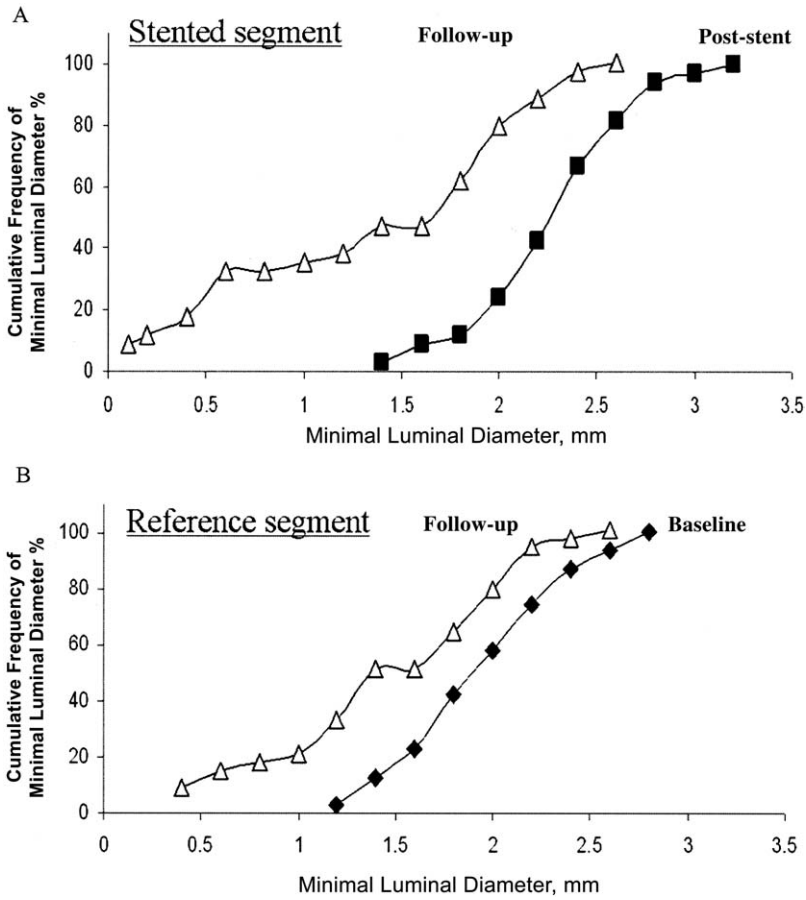

Figure 1. Cumulative frequency of minimal luminal diameters (MLDs). The cumulative frequency distribution curve of MLDs of: **(A)** stented segment, immediately after stent implantation and at follow-up; **(B)** reference, non-stented segment at baseline and at follow-up angiogram.

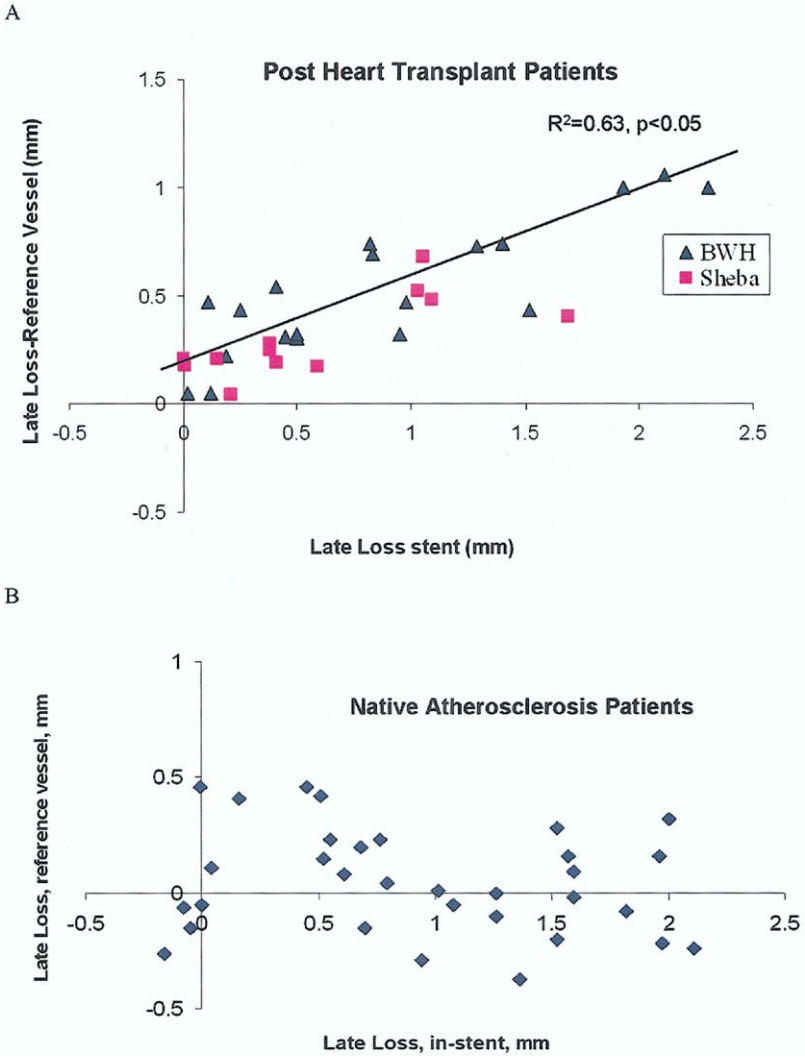

Figure 2. Scatter plot shows correlation between in-stent late loss and non-intervened, reference segment late loss: **(A)** heart transplant patients and **(B)** native atherosclerosis patients. For each individual post-transplant patient, in-stent late lumen loss was closely coupled to late lumen loss of the individual matched non-intervened segment, in both the Sheba Medical Center and Brigham and Women's Hospital (BWH) patient populations. In contrast, no such coupling of in-stent and reference vessel late loss was found in native atherosclerosis patients.

lesions were similar between the 2 groups. Interestingly, at follow-up angiography, the non-PCI lesions from patients who developed ISR had similar LL (−0.01 ± 0.17 mm) compared to the non-PCI lesions of patients without restenosis (0.03 ± 0.27 mm, p = 0.62). All native atherosclerosis (non-CAV) patients displayed minimal progression of atherosclerosis in the non-PCI segments. This is in marked contrast to the disease progression in non-PCI CAV lesions (Table 2). Furthermore, plotting the in-stent late loss with reference segment late loss on a patient-by-patient basis failed to show any correlation (Fig. 2B), in marked contrast to the findings in stented CAV patients.

Long-term follow-up. The 14 patients exhibiting in-stent angiographic binary restenosis were followed clinically for 29.7 ± 11.1 months after PCI. There were 6 deaths (42.9%), all due to graft organ failure. In contrast, there were only 2 deaths (18.2%) in the 11 patients free of restenosis, followed for 36.3 ± 18.0 months after PCI. The causes of death in the non-restenosis group were graft failure (n = 1) and malignancy (n = 1, p = 0.06, comparing cardiac death for patients with and without restenosis). Hospitalization for acute myocardial infarction (MI) occurred in 4 of the ISR patients and in none of the non-restenosis CAV patients. The combined occurrence of cardiac death or MI during follow-up was significantly higher in the group of patients with angiographic ISR (53.8% vs. 9.1%, p = 0.03).

Histopathology. Stented and non-intervened coronary segments of 2 patients after heart transplantation were available for detailed histologic analysis.

CASE 1. A 52-year-old, post-heart transplant woman with CAV underwent stenting of a ramus intermedius in November 2002 (Fig. 3). Repeat angiography in May 2003 revealed focal ISR in the ramus intermedius and significant

disease progression in the non-intervened mid- and distal segments of the left anterior descending coronary artery (Fig. 3). Although both lesions were successfully managed with PCI, the patient suffered an anterior MI 7 months later and expired.

Histologic examination of the stented ramus intermedius and a non-stented diagonal branch artery are shown in Figure 4. Marked neointimal thickening with resultant narrowing of the bare-metal stent lumen was evident, and diffuse intimal hyperplasia impinged upon the non-intervened diagonal lumen as well. The intimal thickening responsible for both lesions (ISR in the ramus intermedius and transplant vasculopathy in the diagonal branch) consisted of fibrotic, collagen-rich, hypocellular matrix with some evidence of inflammatory cell invasion (Fig. 4). Notably, severe adventitial thickening and fibrosis were present in both the stented and the non-intervened artery.

CASE 2. A 39-year-old, post-heart transplant man underwent left circumflex stenting in 1998 and was noted to have progressive CAV and non-critical ISR during follow-up angiography. Out-of-hospital sudden death occurred in 2003.

The stented circumflex artery and non-intervened obtuse marginal branch were available for histological analysis (Fig. 4). Similar to Case 1, severe ISR in the circumflex artery and diffuse intimal hyperplasia in the non-stented obtuse marginal branch were evident. Again, histologic staining demonstrated a fibrotic, collagen-rich, hypocellular neointima with inflammatory cells in both the restenotic lesion and the native non-intervened coronary segments.

DISCUSSION

We report a novel strong association between in-stent neointimal proliferation (restenosis) and progression of coronary artery disease in patients after heart transplantation, which is markedly absent in a control group of stented native atherosclerosis patients. Clinically, ISR accompanied by aggressive CAV progression was associated with poor long-term outcomes after heart transplantation. Angiographic measures showed close coupling on a patient-by-patient basis between ISR and coronary lesion progression at sites remote from the stent, only in CAV patients, possibly suggesting common underlying mechanisms. Post-mortem examination of arteries from 2 patients demonstrated similar histopathological characteristics within restenotic lesions and non-stented CAV sites.

Previous studies of PCI in CAV. Initial experience with balloon angioplasty as a treatment for CAV established the feasibility and safety of percutaneous transluminal coronary angioplasty in this setting but was discouraging because of high restenosis rates (15). Coronary stenting with bare-metal stents, superior to balloon angioplasty in treating native coronary artery disease (16), has also favorably influenced long-term patency after PCI in patients with CAV

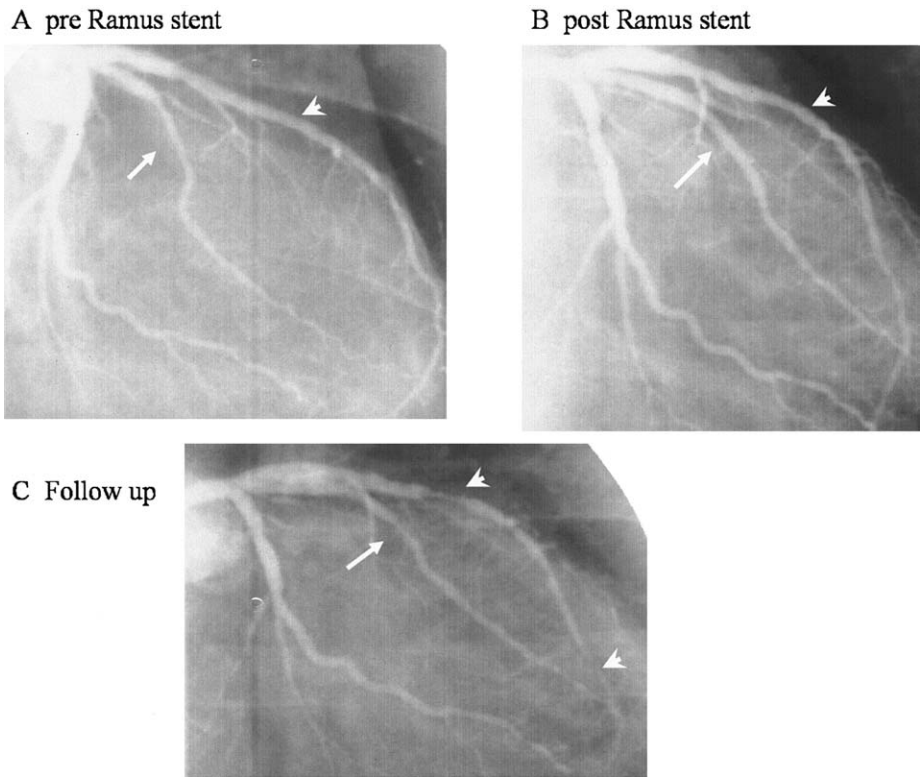

Figure 3. Stenting and follow-up angiograms of Case 1: **(A)** angiogram showing significant stenosis of the ramus intermedius **(arrow)** and minimal irregularities of the reference left anterior descending artery segment **(arrowhead)**; **(B)** post-stent angiogram showing good angiographic result after deployment of a bare-metal stent **(arrow)**; **(C)** repeat angiogram, 6 months after stenting, showing focal in-stent restenosis of the ramus **(arrow)** with significant disease progression in the non-intervened mid- and distal portions of the left anterior descending artery **(arrowhead)**.

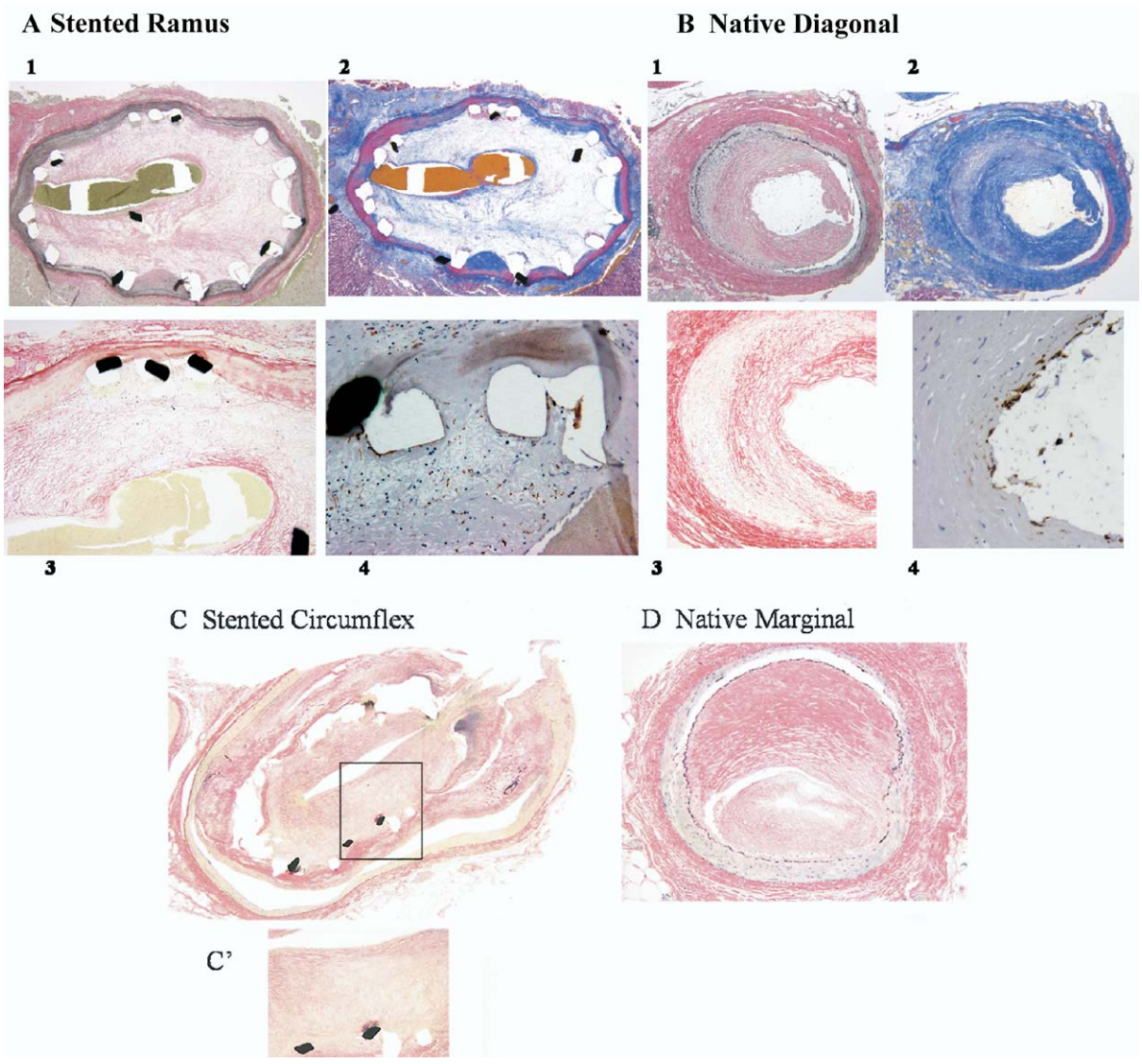

Figure 4. Photomicrographs show: **(A)** Ramus intermedius stent; **(B)** non-intervened, diagonal branch of Case 1 patient. **1)** Verhoeff tissue elastin stain, **2)** Carstair's fibrin stain, and **3)** Sirius red collagen stain demonstrate: in **A**, severe in-stent restenosis and in **B**, diffuse cardiac allograft vasculopathy with similar-appearing intimal thickening consisting of fibrotic, collagen-rich, hypocellular matrix with adventitial thickening and fibrosis in both the stented and the non-intervened artery. **4)** Immunohistochemical CD-68 staining (positive reaction color is **brown**) showing macrophage infiltration in both stented segment neointima **(A)** and non-intervened allograft vasculopathy **(B)**. Photomicrographs (Verhoeff tissue elastin stain) of the circumflex artery stent **(C)** and non-intervened, marginal branch **(D)** of Case 2, and high-power view of the in-stent restenosis neointima **(C')**; both in-stent restenosis and marginal branch transplant vasculopathy demonstrate similar fibrotic hypocellular neointima proliferation.

(3,5,7). Doshi et al. (7) retrospectively described their experience with coronary stenting at 2 medical centers and reported that 9 of 11 lesions treated with stents were patent at follow-up. Benza et al. (3) recently reported 8-month angiographic restenosis rates of 39% in 73 lesions, consistent with our findings of angiographic restenosis in 37.8% of lesions after 1 year.

Correlation of ISR with CAV progression. Of particular interest is our finding, through core lab angiographic evaluations of patients from 2 centers with busy heart transplant programs, of the close association between development of ISR and CAV progression in a control non-stented segment from the same patient over the same time period. Patients with ISR also exhibited marked CAV disease progression, and there was a close continuous correlation across all patients, with or without restenosis, between LL in the stented segment and in the non-treated control sites. This coupling between ISR and non-intervened coronary artery disease was unique to post-transplant patients and notably absent in a cohort of native atherosclerosis patients undergoing PCI with angiographic follow-up. Furthermore, the long-term prognosis of patients with restenosis and CAV progression was significantly worse than that of heart transplant patients without evidence of restenosis, despite similar baseline clinical characteristics.

CAV progression and long-term survival. The development of CAV is a major clinical concern because of its progressive nature and threat to long-term cardiac allograft

survival. Once mild CAV is identified angiographically, the likelihood of progression to severe disease within 5 years is increased significantly (17). Furthermore, approximately 50% of patients noted to have moderate coronary lesions on their annual angiogram will have disease progression a year later, and remain at an increased risk of sudden death and need for revascularization (1,18).

Recently, a multicenter intravascular ultrasound (IVUS) study suggested that progression of intimal thickening in the first year after transplantation appears to be a reliable surrogate marker for development of late angiographic CAV, with subsequent increased rates of MI and mortality (19). A non-randomized retrospective analysis of patients with angiographically evident CAV noted that allograft survival was not altered by PCI (combining both balloon angioplasty and stenting procedures) or medical therapy (2).

Our finding of poor clinical outcomes in CAV patients with ISR (related to CAV but not to the restenosis per se) is consistent with these observations. Our angiographic observation of the close correlation between restenosis and disease progression at remote coronary segments, may permit better selection of revascularization options (bypass surgery vs. drug-eluting stents [DES] vs. bare-metal stents) based on the rapidity of a given patient's disease progression. Systemic therapy aimed at modifying CAV may be particularly appropriate in this subgroup of patients. In particular, a subgroup of patients with aggressive CAV may be poorly served by PCI because of high restenosis rates with concomitant rapid CAV progression at non-intervened coronary segments. Prospective identification of such patients may call for therapeutic options other than, or in addition to, PCI. What effect DES treatment of obstructive or non-obstructive focal CAV will have is of great interest. Many current and future DES are employing macrolide antibiotics (sirolimus, everolimus, and zotarolimus, among others), and there is reason to expect a beneficial effect on LL and restenosis in CAV patients, as has been seen in atherosclerosis patients. However, as a stand-alone focal treatment, this may not translate into long-term clinical benefit in patients at risk for restenosis, as these patients suffer from rapid CAV progression elsewhere in the coronary vasculature.

Pathophysiology features of ISR and CAV. Cardiac allograft vasculopathy is a diffuse, proliferative disease of the coronary neointima, the pathogenesis of which is not fully understood. A growing body of literature supports a paradigm whereby intimal thickening is a consequence of multifactorial endothelial damage from both immune and non-immune causes, followed by an increased inflammatory response driving vascular smooth muscle cell proliferation (1,8,20–22). This process is clearly distinct from conventional atherosclerosis. In-stent restenosis in native coronary artery disease, likewise, is pathophysiologically dissimilar from de novo atherosclerosis. Indeed, in-stent neointimal proliferation is thought also to involve endothelial damage, vascular smooth muscle cell proliferation/migration, and inflammation (14,23,24).

In the present analysis, we were able to examine simultaneously the histopathology of ISR and CAV from 2 heart transplant patients. While these data are limited in number and lack a full analysis of cellular and humeral inflammatory response, they provide a side-by-side histopathology view of ISR and concomitant CAV. Severe in-stent intimal proliferation paralleled substantial intimal thickening of a non-stented segment in both patients. The CAV and restenotic segments shared common histological features of concentric neointimal hyperplasia without any significant lipid or foam cell component. Both stented and non-stented segments had a notably fibrotic neointima, with collagen-rich elements and the presence of some inflammatory (CD68+) cells. Marked adventitial thickening and fibrosis were also observed in both. A single previous histologic description of ISR in CAV noted a paucity of inflammatory cells with marked hypocellularity and similar collagen-rich fibrotic elements in the in-stent neointima (25). Interestingly, Hognestad et al. (26) recently compared immune activation in blood samples from a small group of patients with native atherosclerosis and transplant vasculopathy undergoing coronary interventions. Although a different immune activation profile was noted between the 2 groups, an inappropriate inflammatory reactivity was found to predispose to restenosis in both groups.

Study limitations. The present observational study is retrospective, non-randomized, and limited to only those patients with severe CAV requiring revascularization. Although we used well-established quantitative angiographic analytic methods, angiography is known to underestimate the extent of CAV, especially in comparison to IVUS. Intravascular ultrasound data were not routinely acquired in the reported patients. Therefore, we cannot exclude a role for negative vascular remodeling in addition to intimal hyperplasia at the non-PCI sites of CAV, especially as different mechanisms of lumen loss may hold sway during the early and late phases after transplantation (27). However, our histologic studies as well as prior reports suggest that intimal hyperplasia rather than negative vascular remodeling was the predominant mechanism of LL ISR and probably CAV. Although non-invasive coronary imaging has a potential role as an alternative to conventional coronary angiography in the surveillance of transplant vasculopathy (28), we do not have such imaging data in our patient population.

The histology data provided are significantly limited in numbers, and although immunostaining for tissue macrophages is presented, this is far from being a comprehensive analysis of inflammatory cellular and cytokine response to stent injury and CAV. Finally, the patients reported underwent PCI before widespread availability of DES.

Conclusions. Coronary stenting in cardiac transplant patients has excellent initial procedural success but high

rates of angiographic restenosis after 1 year. A strong correlation exists between angiographic progression of CAV at a non-PCI site and ISR after heart transplantation, in marked contrast to the lack of any such association in a control group of native atherosclerosis patients undergoing stenting with similar angiographic follow-up. Finally, patients with restenosis have greater cardiac mortality related to rapid CAV progression than those without restenosis. The preferred treatment modality for patients with rapidly progressive CAV remains enigmatic, and may continue to be so despite improvements in PCI outcomes, which DES may bring. Treatment strategies for heart transplant patients with CAV, particularly rapidly progressive CAV, need to address the widespread progressive nature of this disease, rather than only the initial focal coronary lesion.

Reprint requests and correspondence: Dr. Michael Jonas, Cardiovascular Division, Brigham and Women's Hospital, 75 Francis Street, Boston, Massachusetts 02115. E-mail: tmjonas@yahoo.com or mjonas@mit.edu.

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